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Treating Fragile X Syndrome and Related Disorders

TREATMENT STRATEGIES FOR FRAGILE X SYNDROME AND RELATED DISORDERS

We are rapidly learning more about the genetic disorder of fragile X syndrome and series of conditions related to Fragile X. We are also seeing great progress in promising therapies under investigation. How will these therapies along with other treatment strategies improve the lives of children and families affected by Fragile X. You are listening to ReachMD XM 157, the channel for medical professionals. Welcome to the clinician's roundtable. I am your host Dr. Mark Nolan Hill, Professor of Surgery and practicing General Surgeon and our guest is Dr. Randi Hagerman, Professor and chair of Fragile X research and Medical Director of the MIND Institute. Medical Investigation of Neuro Developmental disorders at the University of California, Davis School of Medicine.

DR. MARK NOLAN HILL:

Welcome Dr. Hagerman.

DR. HAGERMAN:

Thank you it is a real pleasure to be on.

DR. MARK NOLAN HILL:

We are discussing treatment strategies for the genetic disorder of Fragile X syndrome and related conditions. Dr. Hagerman what is the relationship between Fragile X and autism.

DR. HAGERMAN:

Well Fragile X is the most common single gene disorder that is known to cause autism and about anywhere from 2% to 7% of individuals with autism will turn out to have a Fragile X mutation most of them will have full mutation of Fragile X that means over 200 CGG repeats on the front end of the Fragile X gene, which is on the X chromosome, but some individuals with the premutation that is they are carriers of a smaller CGG trinucleotide repeat. They have between 55 to 200 CGG repeats on the front end of this gene and the premutation can cause a variety of disorders. It can cause autism and ADHD symptoms in young children particularly boys with premutation, although most individuals with premutation have normal intellectual abilities. Those with the full mutation particularly boys with full mutation usually have much more significant developmental delays, mental retardation, or intellectual disability, girls with a full mutation only about 30% have mental retardation, but the rest can have emotional problems or learning difficulties in school even though their IQ can be in the normal range. So there is whole spectrum of involvement from both the premutation and the full mutation, but both types of mutations can include autism. So that when a physician sees a child with autism the Fragile X DNA test should be the first tests that is ordered.

DR. MARK NOLAN HILL:

Is this a difficult diagnosis to make?

DR. HAGERMAN:

No, not at all. Clinically, the diagnosis is made looking at some physical features. Sometimes they can

have prominent ears or hyper-extensible finger joints, sometimes not. They can look very normal, but they usually have behavioral problems like anxiety, poor eye contact, some hand flapping, or unusual hand mannerisms, and usually they are delayed in their speech, although their speech can be real repetitive like they tend to ask the same question again and again. They are usually hyperactive and easily hyperaroused and that is what most of the interventions are targeted to.

DR. MARK NOLAN HILL:

If a child has diagnosis of Fragile X is there automatic screening for the parents and the grandparents?

DR. HAGERMAN:

Yes, once you have a child identified with a Fragile X mutation either pre or full. For a full mutation child, the mother is the carrier because it only expands to a full mutation when it passes through a female and then of the mother who is the carrier it could be either one of her parents who is the carrier. We often times see in the grandparents generation is tremor, ataxia, balance problems, and also neuropathy and these are neurological symptoms that are associated with premutation in aging carriers in 50, 60, 70, and we call this the Fragile X associated tremor ataxia syndrome or FXTAS.

DR. MARK NOLAN HILL:

Are there drugs used at all for treatment in a child with Fragile X?

DR. HAGERMAN:

Oh, absolutely. Usually these individuals have hyperactivity, anxiety, autism or autism spectrum disorders. So we are usually using a stimulant medication, an SSRI or serotonin agent for the anxiety a stimulant for the ADHD symptoms, but one of the best medications out there is an atypical antipsychotic called Abilify or aripiprazole and this helps to stabilize mood. We usually use it in a real low dose at bedtime, it helps to stabilize mood, decrease anxiety, improve aggression if aggression is a problem and treat ADHD symptoms. The most exciting thing about treatment though has to do with targeted treatments for Fragile X.

DR. MARK NOLAN HILL:

What does that mean?

DR. HAGERMAN:

Well, we know a lot about the neurobiology and Fragile X syndrome and we know that a certain pathway in the brain called the mGluR5 pathway is dramatically up regulated in Fragile X syndrome. It is because the Fragile X protein FMRP is the inhibitor for this pathway and so when the Fragile X protein is not there as in Fragile X syndrome this pathway gets up regulated, so we are using what we call mGluR5 antagonist now. We are beginning treatment trials of these medications that can reverse the neurobiological abnormality. These are medications that are approved by the FDA or regulatory agents in other countries to be tried as targeted treatment for Fragile X and we think that they are going to be very helpful.

DR. MARK NOLAN HILL:

If you have just joined us you are listening to the Clinician's Round Table on ReachMD XM 157. I am your host Dr. Mark Nolan Hill and our guest is Dr. Randi Hagerman, Professor and Chair of Fragile X research and Medical Director of the MIND Institute. Medical Investigation of Neuro Developmental disorders at the University of California, Davis School of Medicine. We are discussing treatment strategies for the genetic disorder Fragile X syndrome and related conditions.

DR. MARK NOLAN HILL:

Dr. Hagerman it seems that the symptoms of many different neuro developmental disorders can overlap with Fragile X. Are we treating the Fragile X per se or are we treating just the symptoms associated with these many different neuro developmental disorders?

DR. HAGERMAN:

Well, the reason why the behavioral genotype is so complex is because the Fragile X protein is a regulator for the expression of many, many other genes and some of these genes are associated with

anxiety or autism or ADHD symptoms, so when the Fragile X protein is missing there is dysregulation of a variety of other systems leading to all other features that we associate with Fragile X syndrome. So they are actually part of Fragile X, but we think Fragile X syndrome as the portal disorder for understanding many other disorders and some of the neurobiology that is dysregulated in many other disorder. So it is a key in to understanding many other neurobiological pathways.

DR. MARK NOLAN HILL:

Such as.

DR. HAGERMAN:

Well for instance pathways associated with autism or anxiety and the new targeted treatments for Fragile X like the mGluR5 antagonist they may be helpful for a subgroup of individuals with autism that have similar glutamate pathways involved and I think that mGluR5 antagonist will be generally very helpful treatments for anxiety in individuals in the general population and that is why many drug companies are quite interested in developing mGluR5 antagonist. Not only could they be reversing the neurobiology of Fragile X, but they might be generally helpful for pretty common disorders like anxiety in the general population.

DR. MARK NOLAN HILL:

What about therapies specifically for Fragile X associated tremors and ataxia syndrome?

DR. HAGERMAN:

Well we are studying that. We actually have treatment paper for FXTAS out there. There are a variety of medications that sometimes can be helpful for instance the neuropathic pain you know they often times get neuropathy in the lower extremities and that can cause a lot of pain and many of these individuals go to Pain Clinics just to treat this neuropathic pain, you know gabapentin and Lyrica. These medications that help different types of neuropathy can also help with FXTAS neuropathic pain. We look at a variety of medications to help with tremor and balance problems. We are looking at doing some research on new targeted interventions that could lower the elevated levels of messenger RNA

that occur in the premutation, but that will take a while to actually get into place for common usage.

DR. MARK NOLAN HILL:

Clearly once you make diagnosis who will be supervising the care?

DR. HAGERMAN:

Well it is interesting when you identify one patient for instance it could be a child with Fragile X syndrome usually the pediatrician sometimes with consultation from say some one in developmental behavioral pediatrics or psychiatry can treat the child with some of the psychotropic meds. The educational and special ed people are usually doing the interventions, the psychologist would be doing the behavioral intervention. If the mother has premature ovarian failure, which commonly can occur in premutation carriers usually her OB/GYN person is treating that and if the grandparents one or the other has FXTAS it would be a neurologist or perhaps the primary care physician, for that older person with consultation from the neurologist who would be giving treatment for that individual. So there are multiple generations involved and every time you identify one person in the family tree who has Fragile X mutation there are multiple others. The geneticist or the genetic counselor can help to give guidance to the primary health care provider regarding, you know counseling for extended family members.

DR. MARK NOLAN HILL:

You have used the terms several times before a premutation, what exactly does that mean?

DR. HAGERMAN:

Premutation means a carrier and it is a small mutation, which means there is an expansion of 55 to 200 CGG repeats on the front end of the gene. Now premutation carriers do have often some medical problems associated with the premutation so the term premutation is actually not a good term it is really a small mutation. It is associated with elevated levels of the messenger RNA or the copy of the gene and that causes an RNA toxicity in neurons and in the ovary leading to neurological problems with aging FXTAS symptoms, premature ovarian failure, and on occasion that can cause some neuro developmental problems even in early development leading to ADHD symptoms and autism or autism

spectrum disorders.

DR. MARK NOLAN HILL:

Are there any background similarities among patients who have Fragile X where they come from, etc?

DR. HAGERMAN:

Actually it has been seen in all ethnic and racial groups who have been looked at. It is particularly high in Israel where about 1 in 100 women has the premutation and I think that is because there was big founder affect in the forming of Israel where the people who went to Israel included more premutation carriers than usual.

DR. MARK NOLAN HILL:

I want to thank our guest Dr. Randy Hagerman. We have been discussing treatments strategies for the genetic disorder Fragile X syndrome in related conditions. I am Dr. Mark Nolan Hill and you have been listening to the Clinician's Round Table on ReachMD XM 157, the channel for medical professionals. Be sure to visit our web site at reachmd.com feature on demand podcast of our entire library. For comments and questions please call us toll free at 888MDXM157 and thank you for listening.

Hi, my name is Dr. Carolyn Clancy I am the director of the agency for health care research and quality or AHRQ and you are listening to ReachMD XM 157, the channel for medical professionals.